tion as a shunt production in some cases of jaundice. Is there any direct evidence for this, or is it just speculation? I might also say that we are intrigued by vague analogies of this shunt mechanism to the early glycine shunt which occurs in purine metabolism. Dr. Fudenberg receives the credit for bringing this diagnosis to the attention of the ward team, first off on looking at the bone marrow and hearing the bare outline of the case. Dr. Fudenberg, would you like to comment about this?

DR. H. HUGH FUDENBERG:† As indicated by Dr. Schmid, pronounced erythroid hyperplasia and decided increase in fecal urobilinogen with normal liver function and no, or only slight, increase in hemolytic rate (mild reticulocytosis, mild shortening of red cell survival time, and normal serum LDH and haptoglobin values) are seen in few, if any, conditions other than the one first described by Israels and termed by him "shunt hyperbilirubinemia." Dr. Berlin has indicated that the name is not the most desirable one because the pigments liberated may come from red cell precursors in the marrow rather than from the liver. Nonetheless, the term *shunt* does imply that the pigment does not come from increased hemolysis of the red blood cells in the peripheral blood.

Perusal of the literature suggests that the cases described by Israels in Canada were complicated by the simultaneous presence of a mild form of hereditary spherocytosis, presumably due to genetic linkage of the two traits. It is in this form that mild hemolysis is present and the form in which spherocytes are seen in the peripheral blood. This was true in the patient presented today. In the patient reported by Klaus and Feine in Germany, spherocytosis was not present and red cell life span was normal. These data suggest that two distinct genetic mutations perhaps involving enzymes at different steps in the same metabolic pathway may give rise to the same clinical syndrome, "shunt hyperbilirubinemia." As you know, several different types of genetic mutation may give rise to adreno-cortical abnormality states which are clinically similar.

DR. SMITH: I think it has been clearly brought out that although the studies reported have certainly indicated the source of the excessive formation of bilirubin, the basic genetic abnormality is unknown.

†Associate Professor of Medicine.

DISORDERS OF BILIRUBIN METABOLISM

RECENT SUMMARIES IN THE LITERATURE

Bilirubin Metabolism:

1: Lester, R., and Schmid, R.: Bilirubin metabolism, New Eng. J. Med., 270:779, 1964.

2. Stanbury, J. B., Wyngaarden, J. B., and Frederickson, D. S. (eds.): The Metabolic Basis of Inherited Disease, Chapter 30, "The Porphyrias." New York: McGraw-Hill Co., 1960.

Shunt Hyperbilirubinemia:

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2. Israels, L. G. et al.: The early appearing bilirubin: Evidence for two components, J. Clin. Invest., 44:42, January 1965.

3. Klaus, D., and Feine, U.: Primary shunt hyperbilirubinemia, German Med. Monthly, 10:89, March 1965.

Sclerosing Cholangitis

DR. PHILIP E. MILLS, JR.*: The patient, a 74-year-old Caucasian man, came to Moffit Hospital because of jaundice. He had been perfectly well until, four months before admission, he began to notice anorexia and fatigue. A month before admission he noticed jaundice, dark urine and pale stools and began to vomit small amounts of clear fluid. He had lost 25 pounds during the preceding six months and had had pruritus for two or three years. He said that pruritus had disappeared with the onset of jaundice. He had been bothered by a low backache for about a year but had not previously had jaundice, and questioning elicited no other symptoms referable to the gastrointestinal tract. He had had no chills or fever and he knew of no exposure to sources of hepatitis. Cholecystectomy had been carried out when the patient was 45 years of age, because of recurrent pain in the right upper quadrant of the abdomen. He was said to have had cholecystitis and cholelithiasis.

The patient smoked one package of cigarettes a day and usually drank two to four highballs a day. The family history and social history were not contributory. On questioning it was brought out that he had had mild increasing dyspnea on exertion and a slight cough productive of small amounts of sputum for several years. He had had nocturia without dysuria for about the same length of time.

On physicial examination the patient appeared

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well-developed and well-nourished. He was icteric but in no distress. Vital signs were within normal limits. Scattered rales were heard in the right lung base. The heart was normal to percussion and auscultation. The liver, which was palpable 7 cm below the right costal margin, was firm, smooth and slightly tender. The spleen was of normal size. The nails were slightly brittle and there was loss of the lunulae; there was one spider angioma and the palms were erythematous.

Laboratory Data: The hematocrit was 51 per cent and the uncorrected sedimentation rate (Wintrobe) was 38. The urine was brown with a one plus reaction for protein. An occasional hyaline cast was present. The stool was pale yellow and guiaic-negative. Total bilirubin was 20.8 mg per 100 ml with 5.6 mg conjugated. Alkaline phosphatase was 11 SJR† units (normal two to six). Glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT), prothrombin time, and creatinine and amylase values were within normal limits. Urobilinogen content in a 24-hour specimen of urine was 1 mg. Fasting blood sugar was 110 mg per 100 ml.

At laparotomy the pancreas appeared normal and the liver was firm and green. The common bile ducts extending into the hepatic radicals were thickened and not dilated. The common bile duct was opened, a biopsy specimen was taken, a T-tube was placed and a cholangiogram was performed.

DR. LLOYD H. SMITH, JR.:‡ May we see the x-ray films?

DR. WARREN RUSSELL:§ There are two pertinent x-ray studies. An upper gastrointestinal series demonstrated an apparent widening of the duodenal loop, which is consistent with a mass in the head of the pancreas. This is not diagnostic but is suspicious. The postoperative T-tube cholangiogram is interesting from several standpoints. There is a slight, suggestive irregularity along one wall of the T-tube but it is not very striking. There is a collection of contrast medium in one of the hepatic ducts which appears to be owing either to a very dilated duct or to some extravasation of the contrast medium. From its appearance, I would suspect the latter. The intrahepatic ducts themselves are tapered a little more than we usually see. The common duct is widely patent and the contrast medium flows into the duodenum without difficulty.

†Shinowara-Jones-Reinhardt units.

‡Professor of Medicine and Chairman, Department of Medicine.

§Assistant Professor of Radiology.

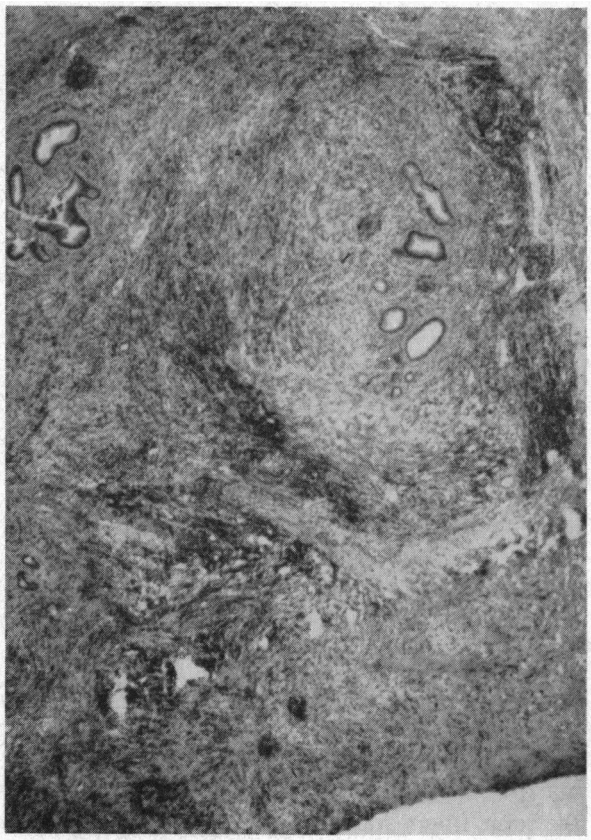

Figure 1.—Frozen section of right hepatic duct. 10x—Hematoxylin and eosin statin.

DR. OSCAR N. RAMBO:* This case prompted a series of frozen sections, none of which in our opinion demonstrated tumor. In a small wedge biopsy of the liver, one can see prominent plugs of bile in cannuliculae but no evidence of cirrhosis. Scattered throughout the liver were fat-filled hepatic cells, a few nuclear abnormalities, some necrotic cells and bile plugs in addition to pigment in Küpffer cells in the sinusoids. The various biopsies, are represented in Figure 1, which is a photomicrograph of a biopsy from "inside the right hepatic duct." The right hepatic duct showed heavy infiltrates of lymphocytes and in some areas these actually formed follicles. Most of the tissue, however, was fairly dense collagenous scar that was infiltrated by chronic inflammatory cells. A closer view of the ductlike inclusions in this biopsy shows very good differentiation and there are, as you know, in the extrahepatic biliary ducts a number of satellite ducts. The findings, from our point of view, are consistent with those described in sclerosing or stenosing cholangitis. This disease

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usually occurs more often in men than in women and there is poor correlation with the presence of gallstones. The origin of this disease is quite obscure. Everything from viruses to the Shwartzman phenomenon has been implicated. I do not know whether there might have been physiologically some stenosis of the segment of duct that contains the T-tube, since this is usually a segmental sclerosis which extends for several centimeters. In summary, this patient had extrahepatic obstruction that had not yet produced biliary cirrhosis, and also inflammation and scarring of several samples of the walls of the common and hepatic bile ducts.

DR. SMITH: Thank you very much. It seemed clear at the beginning that this patient had a surgical problem, but as it turned out it was surgical only in diagnosis. We have called upon Dr. Frank Moody to discuss this problem, particularly the pathogenesis, diagnosis and prognosis.

DR. FRANK G. MOODY:† Primary sclerosing cholangitis seems to be a respectable diagnosis in this patient but it was of interest to me that in his medical work-up this diagnosis was not mentioned, and I suspect this was due to a lack of publicity in the medical literature. But even with a very loose classification there are approximately 35 cases reported in the English literature. My own experience was with two cases at the Cornell University Medical Center. Clinically, this disease presents as progressive jaundice, usually unassociated with pain characteristic of biliary tract disease. However, with close questioning there is usually a complaint of mild discomfort in the epigastrium or in the mid-back, as in the present case. Hepatomegaly is always associated with this condition. The obstructive nature of the icterus is confirmed chemically, with the alkaline phosphatase decidedly elevated and the transaminase normal. Question usually arises as to whether this is obstruction at the level of the cholangioles or in the extrahepatic biliary tree. The differential diagnosis rests among infectious hepatitis in its cholestatic phase, neoplasm, or possibly inflammation, if gallstones are present and the patient has a known history of biliary tract disease or previous biliary tract operation. Because of the insidious onset of jaundice and the frequent presence of a palpable fullness in the epigastrium or a widening of the duodenal loop, exploratory operation often is carried out. At operation the common duct or the common hepatic duct, whichever segment happens to be involved, is a white, thickened, irregular fibrous cord. It feels very much like a thrombosed varix. On incision into the duct, the wall is extremely thick and fibrotic, the lumen is usually of pinpoint size and there usually is some normal-appearing bile within this lumen. Cultures taken in a few cases have grown B. coli.

In the present case there was no bile within the lumen of the duct, but probing into the common hepatic duct did produce a small spurt of normal-appearing bile. In most cases the lumen of the bile duct is smaller than that which we have seen in this particular patient. Biopsy of the specimens of the duct usually show a chronic inflammatory process, and the liver usually is much as Dr. Rambo described it in this particular case.

Postoperatively, in many of the patients, jaundice slowly subsides and they have what appears to be a permanent remission of the disease. Others go on to progressive hepatic failure regardless of treatment.

In a patient whom I followed for a period of four years, the T-tube was left in for a year. Liver function studies never returned to normal but he was not icteric. After removal of the T-tube, he continued to have mildly abnormal results of liver function tests. I encountered a second patient who had had a T-tube in place for four years. It was plugged with calcareous debris and was not functioning. After the tube was removed the patient did quite well.

There is some question as to whether we are dealing with a disease *per se* or a nonspecific reaction of the biliary tree. We know that the bile ducts react this way to injury of any type and occasionally we see this kind of process after operative injury to the duct in removal of the gallbladder. Patients with carcinoma of the bile ducts also have reaction of this type. In fact, one patient who was observed over a period of five and a half years was of this category. He had been operated on three times to maintain a patent biliary tree, the liver biopsy on each occasion demonstrating chronic inflammation. At autopsy a bile duct carcinoma was observed.

It is possible that this disease may represent an auto-immune phenomenon, and some evidence can be mustered to support that possibility. Plasma cells or lymphocytes have been described around the cholangioles within the liver and also within the wall of the extrahepatic ducts, but it is not known whether these are immunologically com-

†Assistant Professor of Surgery.

petent cells. In addition, there is a fairly high association of other diseases that are thought to be related to auto-immunity. In the 25 cases reported since 1954, six of the patients had ulcerative colitis and one had regional ileitis; two had retroperitoneal fibroplasia and another had thyroiditis. Also significant in this regard is that a good response to steroid therapy has been reported in some patients. Two patients whom we have followed did not have steroids and did remarkably well. There are reports in the literature of cases in which patients who did not have T-tube drainage had good relief of symptoms with steroid therapy. One might speculate that the steroids are either interfering with some kind of antigen-antibody process or are nonspecifically suppressing the inflammation associated with this particular disease.

DR. SMITH: We have time for a comment or two on this interesting disease. Dr. Schmid, would you like to make any comment at this time?

DR. RUDI SCHMID:* I wonder why patients with this disease remain jaundiced after good bile flow has been established through a T-tube?

DR. MOODY: I believe the T-tube may be therapeutic, but I am reluctant to say so because I really cannot support such a statement. The patients who have had a good response have had T-tube drainage. At operation it is usually necessary to dilate the duct a little to establish drainage.

DR. SMITH: Does the evidence of inflammation in the duct disappear following T-tube drainage?

DR. MOODY: There has not been adequate information on this point.

Editor's follow-up note: After operation the patient had a wound infection which responded well to antibiotic treatment. He was discharged with prescription of prednisone, 5 mg per day. On the day of discharge the serum bilirubin level was 3.6 mg per 100 ml and alkaline phosphatase was 8 units. Three months later he was feeling much better and at that time the serum bilirubin was 1.0 mg per 100 ml but alkaline phosphatase was 18.4 units. A T-tube cholangiogram done at this time showed persistence of the stricture in the left hepatic duct.

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SCLEROSING CHOLANGITIS

RECENT SUMMARIES IN THE LITERATURE

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3. Schwartz, S. I., and Dale, W. A.: Primary sclerosing cholangitis, Arch. Surg., 77:439-451, 1958.